APPLICATION FOR UNITED STATES LETTERS PATENT

FOR

OPTIMIZATION OF MULTI-DIMENSIONAL TIME SERIES PROCESSING FOR
SEIZURE WARNING AND PREDICTION

BY

J. CHRIS SACKELLARES
LEONIDAS D. IASEMIDIS
DENG-SHAN SHIAU
LINDA DANCE

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STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[001]   The research and development effort associated with the subject matter of this patent application was supported by the Department of Veterans Affairs and by the National Institute of Biomedical Imaging and Bioengineering of the National Institutes of Health (NIBIB/NIH) under grant no. 8R01EB002089-03.

RELATED PATENTS

[002]   This patent application relates to commonly assigned U.S. Patent No. 6,304,775, which issued on October 16, 2001. It is incorporated herein by reference in its entirety.

FIELD OF INVENTION

[003]   The present invention involves the field of signal processing. More particularly, the present invention involves the processing of time series signals associated with multidimensional systems, such as the electrical and/or electromagnetic signals generated by the brain.

BACKGROUND

[004]   A multidimensional system is a system that exhibits behavior autonomously or as a function of multiple variables in response to a system input. A chaotic system is one that exhibits chaotic behavior (i.e., behavior characterized by random responses) during normal operation. The brain is an example of a multidimensional system that also exhibits chaotic behavior during normal operation. In a relatively significant percentage of the human population, the brain experiences periodic, abnormal episodes characterized by non-chaotic behavior. This abnormal behavior may be caused by a wide variety of conditions. Epilepsy is one of these conditions.

[005]   Epilepsy is a chronic disorder characterized by recurrent brain

dysfunction caused by paroxysmal electrical discharges in the cerebral cortex. At any given time, Epilepsy affects approximately 50 million people worldwide. If untreated, an individual afflicted with epilepsy is likely to experience repeated seizures, which typically involve some level of impaired consciousness. Some

5   forms of epilepsy can be successfully treated through medical therapy. However, medical therapy is less effective with other forms of epilepsy, including Temporal Lobe Epilepsy (TLE) and Frontal Lobe Epilepsy (FLE). With TLE and FLE, removing the portion of the hippocampus and/or cerebral cortex responsible for initiating the paroxysmal electrical discharges, known as the epileptogenic focus,

10   is sometimes performed in an effort to control the seizures.

[006]   For quite some time, the medical community has attempted to develop techniques that provide seizure prediction and/or seizure warning, where seizure prediction will be understood to involve a long-range forecast of seizure-onset time, and seizure warning will be understood to involve a long-range

15   indication of conditions conducive to an impending seizure. Any such technique would certainly have numerous clinical and non-clinical application. For example, in order to more effectively treat certain Epilepsy patients, such a technique might be used in conjunction with a device, perhaps an implanted device, designed to deliver a dosage of anti-seizure medication into the patient's bloodstream for the

20   purpose of averting an impending seizure.

[007]   In another example, such a technique could be used during pre-surgical evaluations to assist in pinpointing the epileptogenic focus, which is to be removed during surgery. It is understood that during a seizure, blood flow to the epileptogenic focus significantly increases. If certain radio-labeled ligands are

25   injected into the patient's bloodstream in a timely manner, it is possible to monitor that increased blood flow using radiography, thereby allowing a physician to accurately pinpoint the boundaries of the epileptogenic focus. A true seizure prediction and/or warning technique would provide an indication of an impending seizure well in advance and provide sufficient time to prepare for and administer,

30   for example, the aforementioned radiography ligand.

[008]   One of the most important tools for evaluating the physiological state of the brain is the electroencephalogram (EEG). The standard for analyzing and interpreting an EEG is visual inspection of the graphic tracing of the EEG by a trained clinical electroencephalographer. However, there is no established

5   method for predicting seizure onset or for providing a seizure warning well before seizure onset by visually analyzing an EEG. Moreover, the use of traditional signal processing techniques on EEG signals has likewise yielded little practical information. These traditional techniques are limited in their effectiveness because the brain is a multidimensional system that produces nonlinear signals with spatial

10   as well as temporal properties. Thus, traditional signal processing techniques employing standard, linear, time series analysis methods cannot detect the spatio-temporal properties that are critical in providing effective seizure warning and prediction.

[009]   Commonly assigned U.S. Patent No. 6,304,775, however,

15   describes systems and methods capable of effectively generating true seizure warnings and predictions well in advance of impending seizures. The systems and methods described in this patent take advantage of the spatio-temporal characteristics exhibited by certain sites within the brain, when compared with the spatio-temporal characteristics exhibited by other sites within the brain, as these

20   characteristics are noticeably different prior to an impending seizure as compared to the spatio-temporal characteristics exhibited by these same sites during seizure free intervals. In fact, these spatio-temporal characteristics may be noticeable hours, and in some cases, days before the occurrence of a seizure. As such, the systems and methods described in U.S. Patent No. 6,304,775 use these differences

25   as a seizure transition indicator.

[0010]   U.S. Patent No. 6,304,775 specifically describes, among other things, a technique that provides timely impending seizure warning (ISW), seizure susceptibility period detection (SSPD) and time to impending seizure prediction (TISP). The technique involves acquiring electrical or electromagnetic signals

30   generated by the brain, where each signal corresponds to a single EEG electrode

or channel. Each signal is pre-processed (e.g., amplified, filtered, digitized) and sampled. This results in a sequence of digital samples for each signal over a period of time, referred to therein as an epoch. The samples are then used to generate a phase space portrait for each signal epoch.

[0011]   For each phase space portrait, a parameter reflecting rate of divergence is computed based on adjacent trajectories in the phase space, where rate of divergence, in turn, reflects the chaoticity level of the corresponding signal. In U.S. Patent 6,304,775, the parameter that is used for this purpose is the short-term, largest Lyapunov exponent (STL_{MAX}).

[0012]   In general, the STL_{MAX} values associated with each EEG signal (i.e., each EEG channel) are compared to the STL_{MAX} values associated with each of the other channels. In U.S. Patent 6,304,775, the comparisons are preferably achieved by applying a T-statistic, which results in a sequence of statistical values, or T-index values, for each channel pair, where a sequence of T-index values represents a level of correlation or entrainment between the spatio-temporal response associated with the two channels that make up each channel pair.

[0013]   The technique, when first employed, goes through an initialization period. During this initialization period, a number of "critical" channel pairs is identified, where a critical channel pair is defined in U.S. Patent 6,304,775 as a pair of channels that exhibits a relatively high level of entrainment (i.e., relatively low T-index values for a predefined period of time) prior to seizure onset.

[0014]   During the initialization period, a patient may experience one or more seizures. After each, the list of critical channel pairs is updated. Eventually, the list of critical channel pairs is considered sufficiently refined, and the initialization period is terminated. Thereafter, the ISW, SSPD and TISP functions may be activated and the T-index values associated with the critical channel pairs are monitored and employed in generating timely ISWs, SSPDs and/or TISPs.

[0015]   Even after the initialization period is over, the list of critical channel pairs is updated following each seizure. Updating the list is important

because the brain does not necessarily reset itself completely after each seizure and because the physiological state of the patient may change over time. As a result, the spatio-temporal characteristics associated with any given channel may change over time. Thus, a channel pair previously identified as a critical channel pair

5   may need to be removed from the list of critical channel pairs, while a channel pair that was not previously identified as a critical channel pair may need to be added to the list and subsequently used in generating a next ISW, SSPD or TISP.

SUMMARY OF THE INVENTION

10   **[0016]** The present invention builds upon U.S. Patent No. 6,304,775. It does so by optimizing the selection/reselection of critical channels, the spatio-temporal responses of which are ultimately used as a basis for generating ISWs, SSPDs and TISPs. The present invention achieves this optimization in several ways.

15   **[0017]** Since the issuance of U.S. Patent No. 6,304,775, it has been determined that disentrainment of the spatio-temporal responses associated with two or more channels is an important factor to consider when selecting critical channels. In U.S. Patent 6,304,775, only entrainment was taken into consideration. Thus, the present invention provides for a more effective selection

20   of critical channels by taking into consideration both entrainment and disentrainment data and, therefore, a more effective generation of ISWs, SSPDs and TISPs.

[0018] It has also been determined that two or more channels may exhibit a significant level of entrainment. Regardless, no seizure follows. In fact, the

25   conditions precedent to issuing an ISW may exist, though no seizure follows. These events where the conditions are the same as the preictal conditions of a true seizure, but no seizure actually develops, are referred to herein as "near seizures." Despite the absence of a seizure, the T-index values preceding these "near-seizure" events are valuable. Accordingly, the present invention provides a more efficient

30   and effective critical channel selection process by taking into consideration

entrainment data associated with all seizure-related events, including seizures and "near-seizure" events.

[0019]   The present invention further optimizes the critical channel selection process by limiting the amount of data that is processed. After detecting a seizure-related event (i.e., a seizure or near-seizure event), the present invention processes a limited amount of statistical data (e.g., T-index values) occurring within a predefined time window preceding and, in the case of a seizure, following the seizure-related event. As such, the processing of this data and the subsequent selection of critical channels is accomplished more quickly and efficiently.

[0020]   Accordingly, it is an objective of the present invention to provide ISWs, SSPDs and TISPs well in advance of seizure onset, based on an efficient and effective selection of critical channels.

[0021]   It is another objective of the present invention to utilize the ISW, SSPD and TISP features of the present invention in conjunction with seizure intervention techniques, such as anti-seizure drug medication intervention therapy and neuro-stimulation therapy.

[0022]   It is still another objective of the present invention to utilize the ISW, SSPD and TISP features of the present invention in conjunction with various in-patient applications, including pre-surgical evaluation and diagnosis procedures.

[0023]   In accordance with a first aspect of the present invention, the above-identified and other objects are achieved through a method of analyzing a multidimensional system. The method involves acquiring a plurality of signals, each representing a corresponding channel associated with a different spatial location of the multidimensional system. A phase space representation is generated for each channel, as a function of the corresponding one of the plurality of signals, and thereafter, a signal profile is generated for each phase space representation, each signal profile reflecting a rate of divergence of the corresponding phase space representation. For a selected predictor, chosen from amongst a number of possible predictors, a signal profile is derived for one or more critical channel groups, each signal profile reflecting a level of correlation

between the channels of each critical channel group. Ultimately, the state dynamics of the multidimensional system are characterized as a function of the signal profile associated with at least one critical channel group.

[0024]   In accordance with a another aspect of the present invention, the above-identified and other objects are achieved through a method of providing seizure warnings. This aspect of the present invention involves, more specifically, acquiring a plurality of time-series signals, each associated with a different location of the brain, and where each signal and its corresponding location constitute a corresponding channel. A spatio-temporal response is generated for each channel as a function of a corresponding one of the time-series signals. Then, a signal profile is generated for each spatio-temporal response, each signal profile comprising a sequence of chaoticity values reflecting a rate of divergence of the corresponding spatio-temporal response. One or more seizure-related events are then detected and, after each, a level of entrainment associated with each channel group for each of a plurality of predictors is determined. Based on the level of entrainment associated with each channel group, a number of critical channel groups for each predictor is determined. A selected predictor is ultimately chosen from amongst the plurality of predictors based on the level of entrainment of the critical channel groups associated with each predictor. Thereafter, the method involves determining when the level of entrainment associated with one or more of the critical channel groups of the selected predictor is statistically significant, and if it is so determined, generating a seizure warning.

[0025]   In accordance with a yet another aspect of the present invention, the above-identified and other objects are achieved through a method of providing seizure warnings. This aspect of the present invention specifically involves choosing a selected predictor from amongst a plurality of predictors and acquiring a plurality of time-series signals, each signal associated with a different location of the brain, where each signal and its corresponding location constitute a corresponding channel. A spatio-temporal response is then generated for each channel as a function of a corresponding one of the time-series signals.

Thereafter, a signal profile is generated for each spatio-temporal response, each signal profile comprising a sequence of chaoticity values reflecting a rate of divergence of the corresponding spatio-temporal response. A determination is then made as to whether the level of entrainment associated with one or more

5   critical channel groups of the selected predictor is statistically significant, and if it is so determined, a seizure warning is generated.

[0026]   In accordance with still another aspect of the present invention, the above-identified and other objects are achieved through an apparatus that provides seizure interdiction. The apparatus includes a plurality of sensors, each

10   configured for acquiring a time-series signal associated with a corresponding location of a patient's brain, and processing means for generating a seizure warning based on the time-series signals. The processing means includes means for receiving the time-series signals, where each time-series signal along with the corresponding location of the patient's brain constitutes a separate channel. The

15   processing means also includes means for generating a phase space representation for each channel as a function of the corresponding one of the plurality of signals; means for generating a signal profile for each phase space representation, each signal profile reflecting a rate of divergence of the corresponding phase space representation; and means for deriving a signal profile for each of a number of

20   critical channel groups associated with a selected predictor, chosen from amongst a number of predictors, where each signal profile reflects a level of entrainment among the channels of each critical channel group. The processing means further includes means for determining whether a level of entrainment associated with one or more critical channel groups of the selected predictor is statistically significant

25   and means for generating a seizure warning if it is determined that the level of entrainment associated with one or more critical channel groups of the selected predictor is statistically significant. A seizure interdiction device is coupled to the processing means, where the seizure interdiction device includes means for delivering antiseizure treatment to the patient if a seizure warning signal is

30   generated.

BRIEF DESCRIPTION OF THE FIGURES

[0027]   The objects and advantages of the present invention will be understood by reading the following detailed description in conjunction with the drawings in which:

[0028]   FIGS. 1(a) - (e) illustrates an exemplary, single channel EEG signal as a patient transitions through the various stages of an epileptic seizure;

[0029]   FIG. 2 illustrates a typical, continuous multichannel EEG segment prior to and during seizure onset;

[0030]   FIGS. 3A-3C are flowcharts depicting techniques for providing early ISW, SSPD and TISP in accordance with exemplary embodiments of the present invention;

[0031]   FIGS. 4A and 4B illustrate the placement and use of different electrodes and electrode configurations;

[0032]   FIGS. 5A and 5B illustrate an EEG signal associated with a representative electrode channel over an epoch and the corresponding phase space portraits containing the attractor reconstructed from the EEG signal using the Method of Delays;

[0033]   FIG. 6 is a real time display of recorded EEG signals, corresponding STL_{max} values or profiles and average T-index values for selected critical channel groups;

[0034]   FIG. 7 illustrates the L_{MAX} profiles associated with each of a representative number of channel pairs;

[0035]   FIG. 8 illustrates a procedure for comparing L_{MAX} profiles (e.g., estimations of T-index profiles) for the representative number of channel pairs shown in FIG. 7;

[0036]   FIG. 9 illustrates the TISP feature in accordance with exemplary embodiments of the present invention;

[0037]   FIGS. 10A and 10B illustrate the T-index profiles associated with two electrode pairs calculated over a 10-day period;

[0038]	FIG. 11 illustrates an on-line system that incorporates the ISW,

SSPD and TISP features of the present invention; and

[0039]	FIG. 12 illustrates a therapeutic intervention system that

incorporates an indwelling device capable of providing ISW, SSPD and TISP in

accordance with the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[0040]	Seizures, including epileptic seizures, are multiple stage events.

The various stages include a preictal stage, an ictal stage, a postictal stage and an

interictal stage. FIGs. 1(a-e) illustrate an exemplary electroencephalogram (EEG)

signal, recorded from an electrode overlying an epileptogenic focus, as a patient

transitions through the various stages of an epileptic seizure. More specifically,

FIG. 1(a) illustrates a time sequence of the EEG signal during the preictal stage,

which represents the period of time preceding seizure onset. FIG. 1(b) illustrates

a time sequence of the EEG signal during the transition period between the preictal

stage and the ictal stage, which include seizure onset. It follows that FIG. 1(c)

then reflects the EEG signal during the ictal stage, that is within the epileptic

seizure, where the ictal stage begins at seizure onset and lasts until the seizure

ends. FIG. 1(d), like FIG. 1(b), covers a transitional period. In this case, FIG.

1(d) illustrates a time sequence of the EEG signal during the transition from the

ictal stage to the postictal stage, and includes the seizure's end. FIG. 1(e) then

illustrates the EEG signal during the postictal stage, where the postictal stage

covers the time period immediately following the end of the seizure.

[0041]	As stated, the preictal stage represents a period of time preceding

seizure onset. More importantly, the preictal stage represents a time period during

which the brain undergoes a dynamic transition from a state of spatio-temporal

chaos to a state of spatial order and reduced temporal chaos. Although it will be

explained in greater detail below, this dynamic transition during the preictal stage

is characterized by dynamic entrainment of spatio-temporal responses associated

with various cortical sites. More particularly, the dynamic entrainment of the

spatio-temporal responses at these various cortical sites can be further characterized by:

    (1)   the progressive convergence (i.e., entrainment) of the maximum Lyapunov exponent values (i.e., L_{MAX}) corresponding to each of the various, aforementioned cortical sites, where L_{MAX} provides a measure of chaoticity associated with the spatio-temporal response of a corresponding cortical site; and

    (2)   the progressive phase locking (i.e., phase entrainment) of the L_{MAX} profiles associated with the various cortical sites.

It will be understood, however, that other measures of dynamic entrainment of the chaoticity profiles may be applied (e.g., among first, second or higher order derivatives of the Lyapunov exponent profiles).

[0042]   As one skilled in the art will readily appreciate, an EEG signal, such as any of the EEG signals depicted in FIGs. 1(a-e), is a time series signal that represents a temporal response associated with the spatio-temporal interactions of a particular portion of the brain where the corresponding electrode happens to be located. Since, the brain is a complex, multidimensional system, EEG signals, and other known equivalents, do not and cannot visibly reflect the true spatio-temporal characteristics exhibited by the brain. Thus, traditional linear and nonlinear methods of processing EEG signals for the purpose of providing seizure prediction and/or warning have proven to be generally ineffective as the critical spatio-temporal characteristics exhibited by the brain during the preictal stage cannot be detected from EEG signals alone. Yet, these critical spatio-temporal characteristics exist long before seizure onset, in some cases, days before seizure onset. As such, these spatio-temporal characteristics exhibited by the brain during the preictal stage are essential to any true seizure prediction scheme.

[0043]   To better illustrate the deficiency of EEG signals, FIG. 2 shows a 20 second EEG segment covering the onset of a left temporal lobe seizure. The EEG segment of FIG. 2 was recorded from 12 bilaterally placed hippocampal depth electrodes (i.e., electrodes LTD1-LTD6 and RTD1-RTD6), 8 subdural

temporal electrodes (i.e., electrodes RST1-RST4 and LST1-LST4), and 8 subdural

orbitofrontal electrodes (i.e., electrodes ROF1-ROF4 and LOF1-LOF4). Seizure

onset begins approximately 1.5 seconds into the EEG segment as a series of high

amplitude, sharp and slow wave complexes in the left depth electrodes,

5   particularly in LTD1-LTD3, though most prominently in LTD2. Within a matter

of seconds, the seizure spreads to right subdural temporal electrode RST1, and

then to the right depth electrodes RTD1-RTD3. Of particular importance is the

fact that the EEG signals appear normal prior to seizure onset approximately 1.5

seconds into the EEG segment.

10   **[0044]**   The present invention involves a technique that is capable of

providing an early, impending seizure warning (ISW). The present invention

provides the early ISW by focusing on the aforementioned spatio-temporal changes

that occur during the preictal stage. Moreover, the present invention provides this

capability even though EEG signals do not manifest any indication of an

15   impending seizure during the preictal stage, as illustrated in FIG. 2. However, in

addition to providing an ISW, the present invention is also capable of providing a

seizure susceptibility period detection (SSPD), that is, the presence of abnormal

brain activity long before the occurrence of a seizure, for example, during an

interictal period days before a seizure. Furthermore, the present invention is

20   capable of providing a time to impending seizure prediction (TISP), wherein the

TISP reflects an amount of time that is expected to elapse before seizure onset.

[0045]   One skilled in the art will appreciate that the present invention has

both clinical and non-clinical applicability. FIGS. 3A and 3B provide flowcharts

illustrating a preferred embodiment of a method that is more likely to be employed

25   in a clinical application. As shown, the method includes an initialization period.

The primary objective of the initialization period is to establish a refined set of

critical channels. After the initialization period, the statistical values (e.g., the T-

index values) associated with the critical channels are continuously analyzed for

the purpose of issuing ISWs, SSPDs and TISPs. This will be explained in greater

30   detail below.

[0046]   One skilled in the art will also appreciate the fact that the method

illustrated in FIGS. 3A and 3B is a computer-based method. The same is also true

of the method illustrated in FIG. 3C. As such, it will be understood that these

methods will be an integral part of a larger, computer-based system, and primarily

implemented in software, firmware or a combination of both. For ease of

discussion, the software, firmware or combination thereof will be referred to

herein as the "seizure warning and prediction algorithm" or simply, the

"algorithm".

[0047]   Looking now at the individual steps associated with the method of

FIGS. 3A and 3B, step 301 represents a setup procedure. During this setup

procedure, the clinician is given the opportunity to select or define various

parameters, parameter values and threshold levels. For example, it is at this point

that the clinician may define the number of electrodes to be used, as well as the

location of each electrode. It will be understood that a number of electrode

profiles may be stored in a memory that is part of, or associated with, the

computer-based system. The user may then select and/or modify one of these

profiles through interaction with a customized user interface, preferably a

graphical user interface (GUI), which would also be part of, or associated with,

the computer-based system.

[0048]   Also during setup step 301, the clinician may be given the option of

selecting, from a list of possible choices, the parameter that is to be used for

measuring the level of divergence (i.e., chaoticity) of each channel's spatio-

temporal response. In a preferred embodiment, the parameter to be used for this

purpose is L_{MAX}, or the "short-term" equivalent thereof, STL_{MAX}. Similarly, the

clinician may be given the option of selecting, from a list of choices, the statistical

test to be used in determining the correlation (entrainment) level of the various

channels. In a preferred embodiment, the statistical test used is the T-test, where

the values produced as a result of applying a T-test are referred to herein as T-

index values. How the STL_{MAX} and T-index values are specifically used in the

method of FIGS. 3A and 3B will be evident from the discussion herein below.

[0049]   In addition to selecting certain desired parameters, the clinician may, during setup step 301, define the value of various thresholds. One such threshold is referred to herein as the disentrainment threshold T_D, where T_D represents a T-index value, above which a corresponding group of channels is

5   considered significantly and statistically disentrained. Another threshold is referred to herein as the entrainment threshold T_E, where T_E represents a T-index value, below which a corresponding group of channels is considered sufficiently and statistically entrained. T_{DIFF} is a value that represents the distance or difference between T_D and T_E, where T_D and/or T_E may be adaptively changed

10   with any change in the patient's state according to the T-index values. The relevance of these thresholds will become more evident from the discussion below.

[0050]   Still other parameters and/or parameter values the clinician may select or define during setup step 301 include the number of channel groups (G), into which critical channels are assigned, and the number of critical channels (K)

15   that can be assigned to a particular critical channel group. Once again, the relevance of the number of critical channel groups (G) and the number of channels per channel group (K) will be evident from the discussion below.

[0051]   It should be noted that some parameters defined by the clinician during setup step 301 may be fixed, while others may be adaptive. A fixed

20   parameter is a parameter that has a value which remains constant. An adaptive parameter is one that has a value which may automatically change over time depending upon one or more factors. By way of example, T_{DIFF} represents a difference in correlation level between a level reflecting entrainment and a level reflecting disentrainment. If, during setup step 301, the clinician assigns values to

25   T_E or T_D such that the value of T_{DIFF} is too small, the result may be an unacceptably large number of false warnings (i.e., an ISW that is not followed by an actual seizure). If T_{DIFF} is too large, the result may be an unacceptably large number of failed warnings (i.e., a failure to generate an ISW prior to an actual seizure). If, however, T_E and/or T_D are adaptable, their values may be

30   incrementally adjusted by the algorithm until the number of failed and/or false

warnings is acceptable.

[0052]   Following setup step 301, the algorithm begins acquiring electrical or electromagnetic signals generated by the brain, as indicated by step 303. In a preferred embodiment, each of these signals corresponds to a single EEG channel, as explained above. Each signal is pre-processed. Pre-processing would typically include signal amplification, filtering and digitization. Each digitized signal is sampled, and for each, a sequence of phase space portraits is generated, where each phase space portrait is based on samples falling in a corresponding time window called an epoch.

[0053]   For each channel, and for each of the sequential phase space portraits associated with a given channel, STL_{MAX} values are computed based on adjacent trajectories in the phase space, where the STL_{MAX} values associated with a phase space portrait of a given channel reflect the rate of divergence or choaticity level of the spatio-temporal signal corresponding to that channel. Average STL_{MAX} values are then computed, where average STL_{MAX} represents an average rate of divergence based on a number of STL_{MAX} values falling within a "sliding" time window. The computation of STL_{MAX} and average STL_{MAX} is explained in greater detail below.

[0054]   The average STL_{MAX} values associated with a phase space portrait of a given channel are then compared to the average STL_{MAX} values associated with a corresponding phase space portrait for each of the other channels. In a preferred embodiment of the present invention, the comparisons are achieved by applying a T-statistic, which takes into consideration the standard deviation of the differences between two channels in a "sliding" time window. As stated, this results in a series of statistical values, or T-index values, for each pair of channels, where the T-index values associated with a given channel pair reflect a level of correlation between the spatio-temporal responses of the two channels that make up the channel pair. The calculation of the T-index values for each channel pair is shown in step 307.

[0055]   In a preferred embodiment, the algorithm continues to execute or

perform steps 303 - 307 unless and until the entire process is terminated (e.g., by ending the EEG recording or external command from the operator). Accordingly, the algorithm will continue to acquire and process the electrical or electromagnetic signals associated with each channel, as set forth above. Further in accordance

5   with a preferred embodiment, and in accordance with well established techniques, the algorithm will, if desired, display through the GUI a graphical representation of various data, including the electrical signals associated with each of or a selected number of channels, the STL_{MAX} values for each of or a selected number of channels, and the T-index values for each of or a selected number of channel

10   groups comprised of the critical channels, as shown in step 309. In addition, the algorithm may store this data in one or more appropriate data files, for future display, reference or analysis.

[0056]   The electrical or electromagnetic signals, as stated, continue to be acquired and processed in accordance with the "NO" path out of decision step 311

15   until the patient experiences a first seizure. After a first seizure, as illustrated by the "YES" path out of decision step 311, the algorithm makes an initial critical channel selection, as illustrated in step 313. What this involves and how this is achieved will be described in greater detail below.

[0057]   The seizure, of course, may be detected using any of a number of

20   techniques. For example, the seizure may be detected by the clinician, who does so by physically observing the behavior of the patient. Alternatively, the seizure may be detected by the algorithm, which may do so by detecting a rapid decrease in a number of T-index values. As stated in U.S. Patent No. 6,304,775, a seizure may also be detected by observing certain EEG signal manifestations indicative of

25   a seizure. Other methods of seizure detection may be employed.

[0058]   If a seizure is detected, the algorithm will, in accordance with a preferred embodiment of the present invention, mark the occurrence of the seizure, for example, by setting a status flag. Also, it will store seizure onset time in memory. The algorithm may set the status flag and store seizure onset time

30   automatically if the algorithm itself detects the seizure. The algorithm may set the

flag and store seizure onset time in response to an action taken by the clinician, where it is the clinician that detects the seizure. Regardless, it is the setting of the status flag that causes the algorithm to make the initial critical channel selection, as indicated in step 313.

5   **[0059]**   In general, the initial selection of critical channels, in accordance with step 313, involves computing an average T-index value for each group of channels for each of a number of predictors, where a predictor is a specific number of critical channel groups (G) in combination with a specific number of channels per channel group (K), given a total number of channels (N). Typically, 10   G will be in the range of 1-5 and K will be in the range of 3-6. When G ranges from 1-5 and K ranges from 3-6, there are 20 possible predictors: G_1K_3, G_2K_3, G_3K_3 ... G_5K_6. For each predictor G_xK_y, the algorithm considers each and every possible combination of "y" channels given a total number of channels N. For example, consider the predictor G_3K_5, where there are 30 total channels (N = 30). 15   For this predictor, G_3K_5, there are 142,506 different ways to group the 30 channels into groups of 5 channels each. A subset of 5 channels may belong to more than one group. For each of these 142,506 channel groups, and for each group of channels for each of the other predictors, the algorithm will compute an average T-index value. The average T-index value for each group, for each 20   predictor G_xK_y, is computed based on the T-index values associated with the channel pairs that make up each corresponding group. It should be noted that the algorithm relies on a limited amount of data, for example, the T-index values within a 10 minute time window preceding, not necessarily immediately preceeding seizure onset, and the T-index values within a 10 minute time window 25   following, not necessarily immediately following seizure onset. The algorithm then determines the most relevant channel groups for each predictor. This determination is based on the aforementioned two sets of T-index values (i.e., the 10 minutes preceding and 10 minutes following seizure onset) in each group, where the selected channel groups exhibiting the lowest average T-index values 30   prior to seizure onset in combination with the condition that the average T-index

values represent disentrainment following seizure onset. The "x" selected groups, for some or all of the predictors G_xK_y, exhibiting the most relevant behavior are identified as critical channel groups. For the predictor G_3K_5, the three (x=3) most relevant channel groups are identified as critical channel groups. The optimal

5   predictor(s) $G_xK_yOpt_N$ will then be identified based on the prediction performance during the initialization period (i.e., 311-331).

[0060]   After the initial critical channel selection, the clinician has an opportunity to accept or reject the selection, in accordance with decision step 315. If the clinician decides to reject the initial selection, in accordance with the "NO"

10   path out decision step 315, the algorithm continues to acquire, process, display and store data until a subsequent seizure occurs followed by an acceptable critical channel selection. The clinician may decide to reject the initial selection for any number of reasons. One such reason is the clinician determines that the seizure was not typical. Consequently, the spatio-temporal response of the channels may

15   not be indicative of a typical seizure.

[0061]   After the initial seizure and after an acceptable critical channel selection, as illustrated by the "YES" path out of decision step 315, the algorithm continues calculating average T-index values for each channel group for each predictor G_xK_y, as shown in step 317. Then, per step 319, the algorithm takes the

20   average T-index values associated with each critical channel group, for each predictor, and compares the average T-index values to one or more of the threshold values defined by the clinician during setup step 301 (e.g., T_D and T_E). In a preferred embodiment, the algorithm also computes for each critical channel group a change in average T-index value, which is then compared to T_{DIFF}. It is

25   anticipated that T_D will be set in the range of 5-8, T_E in the range of 3 or less. T_{DIFF} may be used as a single independent parameter in the range of 2-7. In a preferred embodiment, the optimal thresholds are determined during the initialization period (i.e., 311-331). It should be noted that the optimal threshold values may be predictor dependent. That is, the optimal threshold value may be

30   different for different predictors G_xK_y.

[0062]   In this invention, a prediction or warning is declared when a
preictal entrainment transition is observed in the T-index profiles of one or more
critical channel groups for one or more predictors $G_x K_y$. As transition depends on
the value of T_E and T_D, determining the value of T_E and T_D is very important. In a
preferred embodiment, the values are adaptively adjusted based on the state of the
patient. For example, the value of T_D may be set equal to the maximum T-index
value in a previous time interval (e.g., a 20 minute time interval). The value of T_E
is then determined as a function of T_D less a preset distance T_{DIFF}. An entrainment
transition is observed if an average T-index profile exceeds T_D and then
subsequently drops below T_E.

[0063]   As in step 309, step 321 illustrates that the algorithm is capable of
continuously displaying, for all or a selected number of critical channel groups,
the average T-index value and the average T-index value compared to one or more
of the aforementioned threshold values. FIG. 13 illustrates a real time display of
recorded EEG signals, the corresponding STL_{MAX} values or profiles and the
average T-index profiles for three selected critical channel groups. This continues
as the algorithm awaits the occurrence of a next seizure-related event, in
accordance with decision step 323, where a seizure-related event includes a seizure
or an entrainment transition event. If the algorithm determines that no seizure nor
an entrainment transition event are occurring, the algorithm continues to acquire,
process, display and store data, as described above, and calculate and compare
average T-index values for each predictor, in accordance with the "NO" path out
of decision step 323. If, on the other hand, the algorithm determines, in
accordance with the "YES" path out of decision step 323, that a seizure-related
event has occurred, the algorithm will reselect and update the critical channel
groups for some or all of the predictors $G_x K_y$ depending upon whether the seizure-
related event was a seizure or an entrainment transition, as determined in
accordance with decision step 325.

[0064]   As stated, the algorithm may determine that a seizure has or is
occurring in any one of a number of ways. In contrast, the algorithm may

determine that an entrainment transition event has occurred. The algorithm may

determine that a new seizure event has occurred by detecting conditions that would

otherwise cause the algorithm to issue an ISW. Thus, if for any predictor G_xK_y,

the average T-index value corresponding to one or more critical channel groups

5   drops below T_E for a predefined, statistically significant period of time, the

algorithm will establish that an entrainment transition event has occurred. The

conditions upon which the issuance of an ISW is predicated will be explained in

detail below.

[0065]   If the algorithm determines that the seizure-related event is a

10   seizure, in accordance with the "SEIZURE" path out of decision step 325, the

algorithm reselects the critical channel groups for all or some of the predictors

G_xK_y. As in step 313, the reselection is achieved based on average T-index values

corresponding to each and every possible channel group for all or some of the

predictors G_xK_y. Again, in accordance with a preferred embodiment, the

15   algorithm only relies on average T-index values in a predefined time window

preceding (e.g., a 10 minute time window not necessarily immediately preceding)

seizure onset, and average T-index values in a predefined time window following

(e.g., a 10 minute time window not necessarily immediately following) seizure

onset. It will be understood that the algorithm may, in addition to relying on

20   average T-index values associated with the present seizure, rely on average T-

index values associated with prior seizure-related events. If so, it is preferable to

apply appropriate weighting factors to the data, such that the average T-index

values associated with the present seizure have a more significant influence on the

reselection of critical channels than T-index values associated with previous

25   seizures and/or near-seizure events.

[0066]   If, instead, the algorithm determines that the seizure-related event is

an entrainment transition event, in accordance with the "entrainment transition"

path out of decision step 325, the algorithm reselects the critical channel groups,

but only for the predictor or predictors whose critical channels exhibited behavior

30   indicative of an entrainment transition event. In a preferred embodiment, the

reselection of critical channels associated with an entrainment transition event

takes into consideration the average T-index values, for each and every possible

channel group, in a predefined time window (e.g., a 20 minute time window)

preceding the determination that an entrainment transition event has occurred or a

5   window mostly preceding but with an overlap after the time the transition event

occurred. Once again, average T-index values associated with prior seizure-

related events may factor into the reselection process, where appropriate weighting

factors are assigned such that the average T-index values associated with the

present entrainment transition event are given more deference in the reselection

10   process than the average T-index values associated with prior events.

[0067]   When the method illustrated in FIG. 3A is first employed, for

instance, when it is used in conjunction with a new patient, there is an

initialization period. The primary purpose of the initialization period is, as

previously explained, to provide a period during which the algorithm may refine

15   and establish the optimal predictor(s) to enable the selection of critical channels

whose behavior is subsequently relied upon for issuing seizure warnings and

predictions. Accordingly, as shown in step 331, the algorithm periodically checks

for some indication signaling the end of the initialization period. Such an

indication may take the form of an electrical signal generated in response to a

20   clinician's input, where the clinician has determined that the optimal predictor(s)

for the critical channel selection is now adequately stable and refined.

Alternatively, the clinician may be given the option during the setup step 301 to

define the initialization period in terms of a predefined number of seizure-related

events (S). If the algorithm makes no such determination, that is, the algorithm

25   determines the initialization period is not over, in accordance with the "NO" path

out of decision step 331, the algorithm continues to acquire, process, display and

store spatio-temporal response data, as described, calculate and compare average

T-index values, and await a next seizure-related event. If, however, the algorithm

determines that the initialization period is over, in accordance with the "YES" path

30   out of decision step 331, the end of the initialization period is marked by the

selection of a particular predictor or predictors G_xK_y and the identification of the critical channels that make up each of the x number of critical channel groups associated with selected predictor G_xK_y, as illustrated by step 333. If, for example, step 333 results in the selection of predictor G_3K_5, three critical channel groups are identified, each containing five critical channels, where these three groups of five critical channels exhibited behavior most indicative of the seizure-related events during the initialization period. The process then transitions over to a post-initialization period as illustrated by the method of FIG. 3B.

[0068] FIG. 3B is, more specifically, a flowchart depicting a method of issuing an ISW, SSPD and/or TISP after the initialization period is over. It will be noted that generating an ISW, SSPD and/or TISP during the initialization period is certainly feasible by using default or clinician selected predictor(s) with corresponding parameters; however, in accordance with the embodiment illustrated in FIGS. 3A and 3B, that is not the case. Consequently, the first step in the method of FIG. 3B is step 341, wherein the algorithm activates the seizure warning and prediction features. These features may be automatically activated by setting a software "switch", by setting a status flag, or by any similar process that causes, thereafter, the algorithm to issue an ISW, SSPD and/or TISP under the appropriate conditions.

[0069] In step 343, the algorithm calculates the average T-index value for all possible channel groups associated with the predictor selected during step 333. However, in accordance with step 345, the algorithm only compares the average T-index values associated with the critical channel groups to the aforementioned threshold values, where the generation of an ISW, SSPD and/or TISP will be based on the result of these comparisons. Again, the data associated with these calculations and comparisons may be displayed through the GUI and stored per step 347.

[0070] The algorithm will continue to execute steps 343-347 and, simultaneously, monitor conditions for indications of a next seizure-related event, as shown by decision steps 349, in much the same way that the algorithm did so

per step 323 in FIG. 3A. If, as shown by the "SEIZURE" path out of decision step 351, the algorithm determines that a seizure is occurring, the algorithm stores the seizure onset time and, thereafter, reselects the critical channel groups corresponding to the predictor selected during step 333. Again, in a preferred embodiment, reselection is based on an analysis of the average T-index values of all possible channel groups associated with the selected predictor over a predefined time window (e.g., a 10 minute time window) preceding seizure onset time and the average T-index values of all possible channel groups associated with the selected predictor over a predefined time window (e.g., a 10 minute time window) following the seizure onset time. The algorithm repeats this process, in accordance with the "NO" path out of decision step 359, until terminated per the "YES" path out of decision step 359.

[0071]   If the algorithm determines that the constraints necessary to issue a warning and/or prediction have been met, in accordance with the "WARNING" path out of decision step 351, the algorithm generates an ISW, SSPD or TISP, as shown in step 353. The algorithm then reselects the critical channel groups of the predictor(s) per step 355, wherein the reselection is, in this instance, based only on the average T-index values of all channel groups associated with the selected predictor over a predefined time period (e.g., a 20 minute time window) preceding or mostly preceding the time of the entrainment transition event. A more detailed discussion of ISWs, SSPDs and TISPs is provided below. Again, the algorithm continues to repeat the process until terminated in accordance with the "YES" path out of decision step 359.

[0072]   It is important to note that in accordance with a preferred embodiment of the present invention, the algorithm continues to reselect and update the critical channel groups for the predictor(s) after each seizure-related event, that is, after each seizure and after each entrainment transition, per steps 355 and 357. Thus, it can be said that the critical channel selection process is iterative and adaptive before and after the initialization period. The reason for doing so is based on observations that seizures are resetting mechanisms of the

brain's spatio-temporal entrainment with the epileptogenic focus, which is the

precursor of an impending seizure. See J.C. Sackellares et al. "Epileptic Seizures

as Neural Resetting Mechanisms," Epilepsia, vol. 38, p. 189, 1997, see also, L.D.

Iasemidis et al., "Dynamical Resetting of Human Brain at Epileptic Seizures:

5   Application of Nonlinear Dynamics and Global Optimization Techniques," IEEE

Transactions on Biomedical Engineering, in press 2003. It is therefore important

to continuously update the predictor(s) with the critical channels, from one

seizure-related event to the next because the brain does not necessarily reset itself

completely after each seizure and, as a result, the spatio-temporal characteristics

10   associated with any channel may change over time. Accordingly, a channel

previously identified as belonging to a critical channel group may now exhibit a

spatio-temporal response that warrants its disassociation from that groups.

Likewise, a channel that was not previously identified as belonging to a critical

channel group may now exhibit behavior that warrants its inclusion. This iterative

15   and adaptive refinement of the critical channels reduces the number of false

warnings and increases the sensitivity to seizure detection and prediction.

[0073]   FIG. 3C is a flowchart depicting a method for generating an ISW,

SSPD and/or TISP in a non-clinical application. As is readily apparent, the

method depicted in FIG. 3C is substantially similar to the method depicted in FIG.

20   3A. One difference, however, is that the non-clinical method depicted in FIG. 3C

does not employ a distinct initialization period. As such, there is no time period

during which the algorithm selects a particular predictor G_xK_y. Instead, the

clinician may make this selection during setup step 361. Alternatively, the

algorithm could provide a default selection. In addition, as there is no

25   initialization period, the seizure warning and prediction features are activated, as

illustrated in step 376, after the acceptance of the initial critical channel selection.

Accordingly, the algorithm will issue an ISW, SSPD and/or TISP in accordance

with the "YES" path out of decision step 383, the "WARNING" path out of

decision step 385, and step 387 if it determines that the corresponding conditions

30   for doing so have been met. Thereafter, the algorithm reselects the critical

channel groups, as shown in step 389, in the same manner as described for step

355 of FIG. 3B. If, instead, the algorithm detects a seizure, in accordance with

the "YES" path out of decision step 383 and the "SEIZURE" path out of decision

step 385, the algorithm will thereafter reselect the critical channel groups as shown

5   in step 391, in the same way the algorithm reselected the critical channel groups in

step 357 of FIG. 3B.

[0074]   The methods depicted in FIGS. 3A-3C are intended to illustrate

general procedures in accordance with exemplary embodiments of the present

invention. The specific techniques, and alternatives thereto, used to implement the

10   various steps will now be described in greater detail.

[0075]   As illustrated in FIGS. 3A and 3C, steps 305 and 363, respectively,

involve the acquisition of electrical or electromagnetic signals generated by the

brain. In accordance with a preferred embodiment of the present invention,

electrodes are used to record electrical potentials, where each electrode

15   corresponds to a separate channel, and where recordings are made using

differential amplifiers. In referential recordings, one of the electrodes is common

to all channels. The electrodes are strategically placed so that the signal associated

with each channel is derived from a particular anatomical site in the brain.

Electrode placement may include, for example, surface locations, wherein an

20   electrode is placed directly on a patient's scalp. Alternatively, subdural electrode

arrays and/or depth electrodes are sometimes employed when it is necessary to

obtain signals from intracranial locations. However, one skilled in the art will

appreciate that the specific placement of the electrodes will depend upon the

patient, as well as the application for which the signals are being recorded.

25   [0076]   FIG. 4A provides a view from the inferior aspect of the brain and

exemplary locations for a number of depth and subdural electrodes. As shown,

the electrodes include six right temporal depth (RTD) electrodes and six left

temporal depth (LTD) electrodes located along the anterior-posterior plane in the

hippocampi. FIG. 4A also includes four right orbitofrontal (ROF), four left

30   orbitofrontal (LOF), four right subtemporal (RST) and four left subtemporal (LST)

subdural electrodes located beneath the orbitofrontal and subtemporal cortical

surfaces. FIG. 4B illustrates the placement of and use of a subdural electrode

array as well as a strip of electrodes on the inferior right temporal lobe.

[0077]   In accordance with an alternative embodiment of the present

invention, magneto-electroencephalography (MEG) may be employed to record the

magnetic fields produced by the brain. With MEG, an array of sensors called

super-conducting quantum interference devices (SQUIDs) are used to detect and

record the magnetic fields associated with the brain's internal current sources.

[0078]   In yet another alternative embodiment, micro-electrodes may be

implanted into the brain to measure the field potentials associated with one or just

a few neurons. It will be understood that the use of micro-electrodes might be

advantageous in very select applications, where, for example, it might be

necessary to define with a high degree of accuracy the location of the epileptogenic

focus prior to a surgical procedure.

[0079]   Steps 303 and 363 in FIGS. 3A and 3C also involve pre-processing

the signals associated with each channel. These pre-processing steps include, for

example, signal amplification, filtering and digitization. In a preferred

embodiment, filters, including a high pass filter with 0.1 to 1 Hz cutoff and a low

pass filter with 70-200 Hz cutoff, are employed. Depending on the application

and/or the signal recording environment, other filters may be employed. For

instance, if the signals are being recorded in the vicinity of power lines or any

electrical fixtures or appliances operating on a 60 Hz cycle, a 60 Hz notch filter or

time varying digital filters may be employed. Pre-processing results in the

generation of a digital time series for each channel.

[0080]   Steps 303 and 363 further involve generating phase portraits, and in

particular, p-dimensional phase space portraits for each channel, where p

represents the number of dimensions necessary to properly embed a brain state. In

a preferred embodiment of the present invention, the p-dimensional phase space

portraits are generated as follows, where p is assumed to be at least seven (7) to

capture the dynamic characteristics of the ictal state, which may be present during

the preictal state. First, the digital signals associated with each channel are

sampled over non-overlapping or overlapping sequential time segments, referred to

herein as epochs. Each epoch may range in duration from approximately 5

seconds to approximately 24 seconds, depending upon signal characteristics such

5   as frequency content, amplitude, dynamic properties (e.g., chaoticity or

complexity) and stationarity. Generally, epoch length increases as stationarity

increases. In an exemplary embodiment of the present invention, a signal may be

sampled approximately 2000 times per epoch, where the epoch is approximately

10 seconds in duration.

10   **[0081]**   The samples associated with each signal, taken during a given

epoch, are then used to construct a phase space portrait for the corresponding

channel. In a preferred embodiment of the present invention, the phase space

portraits are constructed using a method called "The Method of Delays." The

Method of Delays is well known in the art. A detailed discussion of this method

15   with respect to analyzing dynamic, nonlinear systems can be found, for example,

in Iasemidis et al., "<u>Phase Space Topography of the Electrocorticogram and the</u>

<u>Lyapunov Exponent in Partial Seizures</u>", Brain Topogr., vol. 2, pp. 187-201

(1990). In general, a phase space portrait is constructed using the Method of

Delays by independently treating each unique sequence of p consecutive sample

20   values, separated by a time delay τ, as a point to be plotted in the p-dimensional

phase space. In an exemplary implementation of the present invention, τ equals 4

samples (20 msec).

[0082]   FIG. 5A shows a 6 second epoch associated with an exemplary

EEG signal at the onset of a seizure that originated in the left temporal cortex.

25   FIG. 5B illustrates, from different perspectives, the corresponding phase space

portrait, projected in three dimensions, for the exemplary EEG signal of FIG. 5A.

The object appearing in the phase space portrait of FIG. 5B is called an

"attractor". The attractor represents the region within the phase space in which

the states of the system evolve and remain confined thereto until the structure of

30   the system changes.

[0083]   Steps 305 and 365 in FIGS. 3A and 3C, respectively, involve quantifying the chaoticity of the attractor associated with each channel. There are, of course, different techniques that can be used to accomplish this. However, in accordance with a preferred embodiment of the present invention, the chaoticity of each attractor is quantified using Lyapunov exponents, which represent the average rate of divergence (i.e., expansion or contraction) between point pairs of trajectories that are in close proximity to one another in the phase space. In multidimensional systems, the number of possible Lyapunov exponents is equal to the dimension (p) of the reconstructed state space. Therefore, quantifying the system's behavior may involve calculating sequences of one or more Lyapunov exponents. For instance, if the number of dimensions characterizing the state space is seven (7), then seven (7) different Lyapunov exponent sequences may be computed in quantifying the chaoticity associated with the system's behavior. However, to strike a balance between chaoticity measurement accuracy and signal processing efficiency, only the largest Lyapunov exponent (i.e., L_{MAX}) is used in accordance with a preferred embodiment of the present invention. Although one skilled in the art will readily appreciate that it may be desirable to utilize more than one Lyapunov exponent (i.e., Lyapunov exponents in addition to L_{MAX}) in order to optimize sensitivity and seizure prediction accuracy. For example, it may be desirable to use more than L_{MAX} for cases where it is essential to predict seizure onset time with the highest possible degree of accuracy.

[0084]   Further, in accordance with a preferred embodiment of the present invention, an L_{MAX} value is ultimately derived for each epoch, thereby resulting in a sequence of L_{MAX} values over time for each channel. This sequence of L_{MAX} values (herein referred to as an L_{MAX} profile) represents the chaoticity of the corresponding channel over time. A more complete explanation regarding the computation and utilization of Lyapunov exponents can be found, for example, in Wolf et al., "Determining Lyapunov Exponents from a Time Series," Physica D, vol. 16, pp. 285-317 (1985) and Eckmann et al., "Lyapunov Exponents from Times Series," Phys. Rev. A, vol. 34, pp. 4971-4972 (1986). In the Iasemidis et

al., publication entitled "Phase Space Topography of the Electrocorticogram and the Lyapunov Exponent in Partial Seizures", a method for computing and utilizing short-term Lyapunov exponents (i.e., STL_{MAX}) is described, wherein the method takes into account the nonstationarity of the EEG data, a feature of paramount

5   importance for the accurate estimation of L_{MAX} from EEG in epileptic patients. The reason this feature is so important is the existence of excessive transients (e.g., epileptic spikes, fast or slow wave transients etc.) in the EEG from such patients.

[0085]   Steps 307, 317 and 319 in FIG. 3A, 343 and 345 in FIG. 3B, and 367, 377 and 379 in FIG. 3C involve evaluating the entrainment of the L_{MAX}

10   profiles, or more specifically, STL_{MAX} profiles. Evaluation may be achieved by calculating the average and standard deviation of the difference over consecutive STL_{MAX} values falling within a "sliding" time window. The length of time associated with the "sliding" time windows is approximately 10 minutes (i.e., a span of approximately 60 epochs). The result is a sequence of average T-index

15   values over time for each channel group of the predictor.

[0086]   In general, step 307 in FIG. 3A and step 367 in FIG. 3C involve comparing the STL_{MAX} profile associated with each channel to the STL_{MAX} profile associated with each of the other channels to determine whether the corresponding pair of signals show signs of entrainment. For the purpose of the present

20   invention, the term "entrain" refers to a correlation or convergence in amplitude and/or phase between measures of two signals that make up a channel pair. Although any number of statistical methods may be employed to quantify the degree of correlation between a pair of signals, a pair T-statistic is employed for this purpose in accordance with a preferred embodiment of the present invention.

25   [0087]   By applying the pair T-statistic, a T-index is derived for each of a number of overlapping or non-overlapping "sliding" time windows for each channel pair, wherein the duration of a time window may vary from approximately 1 minute to 20 minutes. As already mentioned, in a preferred embodiment of the present invention, the duration of these "sliding" time windows is approximately

30   10 minutes. Optimally, the length of time associated with these time windows

must capture, with sufficient resolution, and a minimum number of computations, the dynamic spatio-temporal transitions during the preictal stage. Since the preictal transitions are ultimately characterized by the progressive entrainment of STL_{MAX} profiles associated with critical channel groups, it is the rate of

5   entrainment between the STL_{MAX} profiles and the level of statistical significance that determines the optimum length of these time windows.

[0088]   FIG. 7 illustrates a comparison between the STL_{MAX} profiles associated with each of a representative number of channel pairs. More particularly, FIG. 7 shows a comparison between the STL_{MAX} profile

10   corresponding to a signal associated with a left temporal depth electrode LTD1 and the STL_{MAX} profile associated with six other representative electrode sites. The six other representative electrode sites are a left orbitofrontal electrode LOF3, a right orbitofrontal electrode ROF3, a left subtemporal electrode LST4, a right subtemporal electrode RST4, a left temporal depth electrode LTD3 and a right

15   temporal depth electrode RTD2. Although FIG. 7 only shows STL_{MAX} profile comparisons for six representative channel pairs, in a preferred embodiment of the present invention, steps 307 and 367 in FIGS. 3A and 3C, respectively, involve STL_{MAX} profile comparisons for all channel pairs. For example, if signals are being recorded at 20 different electrode sites, procedural step 307 would typically

20   involve 190 Lmax profile comparisons, as there are 190 different channel pairs.

[0089]   FIG. 8 illustrates the T-index profiles that correspond with the six channel pairs illustrated in FIG. 7. From the T-index profiles illustrated in FIG. 8, it is evident that the STL_{MAX} profiles associated with each channel pair all progressively become entrained during the preictal stage (i.e., during the 0-60

25   minute time frame), while each channel pair becomes progressively disentrained during the postictal stage. However, the rate and degree at which the STL_{MAX} profiles become entrained and disentrained vary. In FIG. 8, the channel pair associated with the electrode LTD1 and electrode LTD3 demonstrates a relatively high level of entrainment (i.e., relatively low T-index values), more so than the

30   other five channel pairs. The channel pair associated with the electrode LTD1 and

electrode RTD2 also shows a relatively high level of entrainment, particularly

during the preictal stage. Although FIG. 8 only shows T-index values 60 minutes

prior to and 60 minutes following seizure onset, the preictal period typically

begins approximately 15 minutes to as much as 2 hours prior to seizure onset.

However, it is extremely important to note that signs of entrainment, such as

reduced T-index values, particularly those associated with critical channels, may

be evident long before seizure onset. In fact, it is possible that critical channels

will exhibit signs of an impending seizure days before an actual seizure.

[0090]   Steps 313, 327 and 329 in FIG. 3A, 355 and 357 in FIG. 3B, and

373, 389 and 391 in FIG. 3C all involve the selection or reselection of critical

channels, or more specifically, critical channel groups. In general, that portion of

the algorithm which controls this section process ultimately seeks to identify those

channel groups which are critical, given the constraints defined by the clinician.

During the initialization period covered by the method steps in FIG. 3A, the

algorithm seeks to identify critical channel groups for all predictor $G_x K_y$, as

explained above. After the initialization period, as covered by the steps in FIG.

3B, and in accordance with the non-clinical method illustrated in FIG. 3C, the

algorithm seeks to identify the critical channel groups associated with at least one

selected predictor.

[0091]   Steps 353 and 387 in FIGS. 3B and 3C, respectively, involve

generating an ISW, SSPD and/or a TISP. The specific techniques employed to

generate an ISW, SSPD and/or TISP, in accordance with these steps, will now be

described in greater detail. The first of these features to be described is the early

ISW feature. In general, an ISW is triggered when one or more critical channel

groups associated with a selected predictor are highly disentrained (i.e., average

T-index values above T_D) and then later they become entrained (i.e., average T-

index values below T_E) for a statistically significant period of time. More

specifically, an ISW is generated when the average T-index values associated with

the one or more critical channel groups, previously above a disentrainment

threshold, fall below a statistically significant entrainment threshold value for a

statistically significant period of time. In a preferred embodiment, that threshold is T_E. Further in accordance with a preferred embodiment, the statistically significant period of time during which the average T-index value must remain below T_E in order to trigger an ISW is typically set somewhere between 0 minutes and 1.5 hours. For example, an average T-index value less than $T_E = 2.09$ for a period of time equal to 15 minutes equates to a 99 percent confidence level that the issuance of an ISW is a valid warning. Of course, it will be understood that the threshold value T_E and the duration which the average T-index must remain below that threshold value may be adaptively adjusted to increase or decrease ISW sensitivity and reduce the incidence of false warnings (i.e., false positives) for any given patient, or reduce the incidence of failed warnings (i.e., false negatives).

[0092]   The ISW may be implemented in any number of ways. For example, the ISW may involve audible warnings or visual warnings or a combination of both visual and audible warnings. In fact, the ISW may involve nothing more than the setting or resetting of an internal software variable or flag, wherein the setting or resetting of the variable or flag triggers a dependent event, such as the automatic delivery of anti-seizure medication. Accordingly, the specific implementation of the ISW will depend on the specific clinical or non-clinical application for which the present invention is being employed.

[0093]   The next feature is the TISP feature. Once the algorithm generates and ISW, the rate of entrainment, that is, the rate at which the STL_{MAX} profiles associated with a critical channel group continue to converge, may be used to estimate the amount of time before seizure onset. In accordance with a preferred embodiment of the present invention, this is accomplished by continuously deriving, for each of the one or more critical channel groups, the slope of the corresponding, average T-index profile over a "sliding" time window, as illustrated in FIG. 9. The point at which the slope intercepts the time (t) axis represents an estimated seizure onset time. Therefore, the difference between the present time and the estimated seizure onset time, along the time (t) axis, represents the TISP. The length of the "sliding" time window may, once again,

vary. Initially, it may be set to a relatively small time interval (e.g., 15 minutes). Thereafter, it may be adaptively optimized for each individual patient.

[0094] The last of the three features is the SSPD feature. Over a period of several hours, if not several days prior to a seizure, or a first of a series of seizures, there is generally a gradual entrainment among certain critical sites. The present invention exploits this to provide the SSPD feature. Specifically, the SSPD feature is, in accordance with a preferred embodiment of the present invention, implemented in much the same way as the ISW feature, that is, by generating a T-index profile for each of the one or more critical channel groups associated with the selected predictor, and by observing those average T-index profiles. The average T-index profiles are typically generated and observed over a period of several hours or days, rather than minutes.

[0095] FIGS. 10A and 10B illustrate the average T-index profiles associated with two different electrode pairs calculated over a 10-day period. It will be understood, however, that similar, average T-index profiles might be generated for critical channel groups consisting of two or more channels. The patient was seizure-free during the first 135 hours of the recording. However, over the subsequent 90 hours, the patient experienced 24 seizures, as indicated by the 24 arrows located along the time (hours) axis.

[0096] FIG. 10A specifically shows a T-index profile associated with a focal electrode RTD3 and a contralateral subtemporal electrode LST4. For this particular channel pair, dynamic entrainment occurred gradually, where the T-index profile values fell below T_E only after the third day of recording. At the onset of the first seizure, resetting of the affected cortical sites (i.e., disentrainment) begins to occur.

[0097] Referring now to FIG. 10B, it is of particular interest that the T-index profile associated with bilateral hippocampal electrodes LTD3 and RTD3 falls below the statistically significant threshold value T_E, approximately one (1) day into the recording, thus indicating that the signals associated with the electrode pair are entrained approximately four (4) days prior to the first seizure.

Moreover, the signals associated with this pair of electrodes remain mostly entrained until the first seizure, after which, the affected cortical sites begin to reset progressively. Again, the present invention exploits this behavior to provide the SSPD feature. It should be noted that due to the time resolution (i.e., hours)

5   used for FIGS. 10A and 10B, resetting after each individual seizure cannot be visualized in these figures.

[0098]   As described above, the methods illustrated in FIGS. 3A - 3C rely on a comparison between the STL_{MAX} profiles of channel pairs, where each STL_{MAX} profile is derived from a signal measured at a corresponding electrode

10   site. In some instances, it may be beneficial to directly compare the STL_{MAX} profiles corresponding with each group of channels for all or the one selected predictor. In such instances, the groups will typically consist of more than two channels and it may not be appropriate to employ a T-statistic. For example, an F-statistic or F-index statistic (i.e., ANOVA statistic) may be employed instead of a

15   T-statistic, if STL_{MAX} profiles associated with groups of three or more channels are being compared. Yet another alternative is to employ neural network technology and pattern recognition techniques to analyze the level of entrainment between groups of two, three or more STL_{MAX} profiles.

[0099]   FIG. 11 illustrates an on-line system 1100 that incorporates the

20   various features of the present invention, as described above. The on-line system 1100 may be used in any number of clinical or non-clinical applications, including diagnostic applications, as well as applications relating to patient treatment. For example, the on-line system 1100 may be used to collect and process EEG or MEG signals for subsequent clinical interpretation (e.g., to analyze and determine

25   seizure propagation patterns). The on-line system 1100 may also be used to alert hospital or clinic staff members of an impending seizure, via a local or telemetry link, so that staff members have adequate time to prevent patient injury or provide timely medical intervention to prevent the seizure itself; to observe the seizure; or to prepare for and administer other procedures that must be accomplished during

30   the seizure, such as the administration of radiolabelled ligands or other substances

required to obtain ictal SPECT, ictal FMRI, or ictal PET images for pre-surgical

diagnostic purposes.

[00100]   In addition to surgical excision of the epileptogenic focus,

current methods for controlling epileptic seizures include pharmacological (i.e.,

antiepileptic drug) therapy. The currently accepted pharmacological approach is to

prescribe fixed doses of one or more antiepileptic drugs (e.g. phenytoin,

phenobarbital, carbamazepine, divalproex sodium, etc.) to be taken chronically at

fixed time intervals. The objective is to achieve a steady-state concentration in the

brain that is high enough to provide optimal seizure control, but low enough to

reduce the risk of side-effects.

[00101]   Given the currently accepted pharmacological approach

described above, FIG. 12 illustrates an alternative, system level embodiment of the

present invention. More particularly, FIG. 12 illustrates a pharmacological

antiepileptic seizure system that includes an indwelling device, such as a real-time

digital signal processing chip 1210, that contains, among other things, an

algorithm that is capable of providing seizure warning and prediction (ASWP), in

accordance with the present invention, as described above. As illustrated in FIG.

12, the ISW, TISP, and SSPD signals generated by the indwelling device 1210 are

forwarded to a controller 1220. The controller 1220 can then trigger the release of

a compound, such as a small dose of an anticonvulsant drug, into the blood stream

of the patient from a stimulator 1230 which contains or is connected to an

indwelling reservoir. The objective, of course, is to release a small quantity of

anticonvulsant drug during the preictal transition stage to abort any impending

seizure.

[00102]   FIG. 12 also illustrates that the therapeutic intervention system 1200

may, in addition to delivering anticonvulsant drug therapy, deliver electric or

magnetic stimulation, for example, through a vagal nerve stimulator. Vagal nerve

stimulators are currently used to deliver electrical impulses to the vagus nerve in

the patient's neck at externally specified intervals, in an arbitrary fashion, with a

predetermined duration and intensity. In contrast, the present invention, in

accordance with the exemplary embodiment illustrated in FIG. 12, delivers an electrical impulse to the vagus nerve in the neck of specified duration and intensity, but the impulse is delivered only during the preictal transition state. To accomplish this objective, the indwelling device 1210 detects the preictal transition

5   state based on dynamical analysis of ongoing brain electrical activity, as described in detail above. When a preictal state is detected, the indwelling vagal nerve stimulator is triggered and an electrical pulse is delivered to the vagus nerve in the neck. It will be readily apparent, however, to those skilled in the art that devices other than vagal nerve stimulators, for example, deep brain stimulators, may be

10   used in conjunction with the present invention to create brain pacemakers for epileptic patients.

[00103]   The present invention has been described with reference to a number of exemplary embodiments. However, it will be readily apparent to those skilled in the art that it is possible to embody the invention in specific forms other

15   than those described above without departing from the spirit of the invention. In fact, it will be readily apparent that the present invention may be employed for other medical (e.g., heart pacemakers, stroke diagnosis and prevention, dynamic brain disorders, etc...), non-medical, non-linear, multidimensional dynamic processes characterized by sudden phase transitions. Accordingly, the various

20   embodiments described above are illustrative, and they should not be considered restrictive in any way. The scope of the invention is given by the appended claims, rather than the preceding description, and all variations and equivalents thereof which fall within the range of the claims are intended to be embraced therein.

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